# MALARIA.

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Thesis for the Degree of Doctor of Medicine

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# M A L A R I A

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Since the time Celsus wrote on Malaria, many theories have been held as to its cause; amongst others, chill, and certain electrical conditions of the atmosphere; but it was difficult to conceive the grave pathological conditions of this disease to be due to either. As early as 1717 Lancisi supposed that Malaria was a disease due to parasitic animalcules, which found their way into the blood; and since then there have not been wanting numerous observers who have from time to time, put forward one form or another of organism as the cause of the disease. These, however, did not attract much attention, till in 1879 Klebs and Tommasi-Crudeli found, in the air and soil of the Pontine marshes, an organism, which, on being injected into the circulation of rabbits, produced phenomena which they believed to be not unlike intermittent fever; and to this organism, the former of these observers gave the name Bacillus Malariae. This organism was for a time very generally accepted as the cause of Malaria. However, it was left for Laveran to clear up the much disputed etiology. The discovery of the Malaria parasite was made on the 6th November, 1880, by the French military surgeon, A.Laveran whilst on active service in Algiers, and he communicated it to the Academie des Sciences in Paris on the 24th October, 1881. Laveran's views have been confirmed by pathologists all over

the world.

To demonstrate the parasite staining is not necessary; the general rules for microscopic examination of the blood are followed. The slide, cover glass, and finger are thoroughly cleansed with soap and water and then in alcohol. The finger is ligatured and slightly pricked and a cover glass applied lightly to the droplet of blood - which should be no bigger than a pin's head - and then placed on the slide. Great care should be exercised to have the corpuscles lying flat on their faces, and not in rouleaux, as the parasite is generally inside the corpuscle and not on its edge. A good immersion lens, a 1/12" is necessary, although Laverau with rather a low power and primitive surroundings achieved his great discovery. The usual form of the parasite will be found lying inside the blood corpuscle, in the shape of an ill-defined, pale, nebulous body, containing dots of black pigment. The following forms are to be met with, singly or in association:-

I. Minute nucleated bodies or spores  which are free in the blood.

II. Small epi- or intra corpuscular bodies  , presumed to be those spores which have attacked the red blood corpuscles.

III. Large intracorpuscular, pigmented, amoeboid bodies 

IV. Sporulating intracorpuscular forms, known as "rosette bodies"   These "rosette bodies", outside the blood corpuscles, break up and become resolved into

the afore-mentioned spores.

V. The "crescent" form  , also inside the red blood corpuscle.

VI. If Malaria blood be observed sometime after it has been drawn from the blood vessels, yet another form is seen, namely, the "flagellated body". This flagellated body never appears or comes into view on the microscope field immediately after the withdrawal of blood from the vessels of the body, but only after the blood has been on the slide for some minutes. It therefore cannot exist as such in the circulation, although potentially it must be represented there in some of the forms already described. The flagellated body is evolved from the crescent body, and from the large intracorpuscular, amoeboid body. Through the kindness of Dr Patrick Manson supplying me with malaria blood from the seaman's hospital, I have been able to watch the crescent form evolve the flagellated body. The crescent is seen to become spherical, and the pigment assumes a peculiar agitated movement, and then a flagellum bursts through the periphery  and after a time it becomes free, and swims about as a free parasite, with vigorous, lashing movements in the liquor sanguinis. In those cases which I had under observation only one flagellum was evolved, but I understand from other observers two, three, or more may be evolved. Dr Manson suggests that these flagellated bodies are destined for the continuation of the species outside

the human body, probably finding their way into the bodies of some suctorial insect, after the manner of the filaria nocturna. Laverau regards the flagella as the mature form of the parasite, whilst the Roman School hold they have no necessary connection with the fever.

With regard to the position which the parasite holds in relation to the red blood corpuscles, Laverau, even in his latest published work "Paludisme", holds to the view that it is extraglobular, though it often attaches itself to a corpuscle and is very frequently to be seen quite free, whilst Marchiafava, Bignami, and the Roman school in general assert that it is essentially endo-globular when it is free, except in the stage of a spore, it is often seen undergoing degenerative processes. My own observations lead me to incline to modestly differ from the great French observer, and to accept the teachings of the Roman school.

Laverau holds the view that the malarial parasite is an individual species whose various shapes are brought about by polymorphism, and that the different types of fever are not caused by different species of parasites. On the other hand, Golgi, and others of the Italian school believe in the presence of several genera or species and varieties of parasites and hold that each type of fever corresponds to a definite species.

For years I searched for this parasite without success, and I left the Tropics ignorant of its appearance. Perhaps this failure was due to the not too minute directions given by Laverau, coupled with not knowing exactly what to look for,

it was not till after my return to London that I was enabled through the kindness of Dr. Manson to satisfy myself concerning this haematozoon. Once recognised, the parasite can be demonstrated in the blood of all patients suffering from Malaria.

Clinicians and Pathologists used to be sorely troubled in trying to find an explanation for the Melanaemia, Anaemia, and the fever paroxysm. . However, since Laverau's discovery, these points have been cleared up. The Melanaemia is explained indubitably by the fact that the parasites transform the haemoglobin by which they are nourished by means of their metabolism into Melanin. The Anaemia by the fact that the infested blood corpuscles are consumed and destroyed by the parasites; hence, the greater number of parasites there are, the more blood corpuscles will be destroyed, and the consequent anaemia will be the more grave. The paroxysm of fever is, according to Golgi, due to the bursting of the sporing bodies; and immense number of spores and most probably also other substances which are formed in the parasites and are poisonous to man, get into the blood, and that these injurious bodies together cause the paroxysm.

Incubation and Course of the Fever:-

The incubation period has generally been stated to be ten to fourteen days, but that it may be five days, or less, can be clearly seen from my own case. I left Liverpool for West Africa on October 4th, and on the 11th touched at the Canary Islands, where I spent an hour ashore. Then, for three weeks

we never touched land, until we arrived at our destination. During these three weeks (and previously, I may state) I enjoyed good health, and as far as I know was in perfect health when I landed in Africa. Five days after disembarking I was attacked with Malarial fever of a severe form. My first warning of what was in store for me, occurred on the morning of the fifth day after my arrival, when I felt a slight aversion to my morning bath, but at no time had I anything approaching to a rigor. Towards evening an overmastering drowsiness and desire to be left alone overtook me. So intense was this feeling, that skirmishing going on a few hundred yards from my quarters failed to interest me. Pain in the back, head, and limbs, furred tongue, vomiting and constipation, with pyrexia were the symptoms. The temperature remained elevated for five days, and kept oscillating between 103° and 105° F. Then it suddenly fell. The convalescence was accompanied with marked anaemia and extreme debility. This may be taken as a typical case in a healthy new-comer. I may note here that all persons on the West Coast, sooner or later suffer from Malaria, and those who are fortunate enough to survive and become "old residents", (I mean by that a period of a few years) state that the sooner a new-comer is affected with his "baptismal" fever the better, as his chances of recovery, owing to his organs being healthy, are greater.

Case II. This occurred in a young man, aged 26 years, who had been resident on the Coast for two years, and may be taken as a type of the Fever as it affects those who have been

previously debilitated by attacks of Malaria. His illness commenced slowly and was not sufficiently severe to force him to bed until the second day when I saw him. His temperature was 102° F., and he had been dosing himself with Quinine. I did not consider his condition grave, and his symptoms were apparently favourable to recovery, with perhaps the exception of his pulse, which was not unnaturally quick, but had a peculiar flabby feel, a character which I afterwards learnt meant mischief and to associate with a grave prognosis. On the third day his temperature was 105° F., and he had been slightly delirious during the night. The fourth day showed no change. On the fifth day it fell to 103° F., and on the sixth to 102 F., and on the seventh day to 100° F.; he now said he felt better, and to me his condition seemed favourable. Suddenly, on the afternoon of the eighth day, his temperature ran up to 110° F.,; he became comatose, and died in a few hours. The temperature rose considerably after death.

Before entering into a discussion of the treatment of Malaria, I may here epitomise the views held as regards the parasiticide action of the salts of Quinine. According to Laverau, the action of this drug prevents the mobile filaments from escaping from their cysts, and makes the haematozoa assume their cadaveric form. The researches of Marchiafava and Bignami lead them to believe that this alkaloid inhibits the nutritive processes which enable the haematozoon to develop and grow, up to the time that it has been ready to undergo segmentation. When once the spores have become free

in the blood plasma, the specific appears to exert a deleterious action on them, and to render them incapable of penetrating into the red blood corpuscles, where alone they seem able to accomplish their life cycle. At any rate, there is no doubt that a generation of spores, on becoming free in the blood plasma sufficiently charged with Quinine, disappears, and proves for the time harmless.

TREATMENT:-

The treatment of Malaria is essentially that of cinchonising the parasite, and the sooner this is accomplished the better for the patient. But before discussing the different methods by which this may be effected, I propose to consider initial purgation, with reference to bringing about the absorption of Quinine by the stomach in as short a time as possible, in order to have the maximum amount of the drug in the circulating fluid in a given time. The extreme rapidity by which Quinine is eliminated by the kidneys renders this imperative so as to obtain its full parasiticide action.

All practitioners in malarious districts agree that an initial sharp purge enhances the value of Quinine. The lamented traveller, Livingstone, a no mean authority on Malaria, always commenced his treatment by giving pills of Jalap, Rhubarb and Calomel. These pills were, by his men, designated "rousers". That Calomel is the most efficient purge for the purpose under consideration, I am, at least, fully convinced, in spite of many excellent authorities who denounce this drug on account, they say, of its lowering properties. I have given it many thousands of times, both to the strong and debilitated,

with splendid results and no after bad effects. I have frequently given patients a purely vegetable purge and generally found the sickness and furred tongue to remain longer, as well as the length of time necessary to bring the patient under the influence of Quinine. Calomel undoubtedly, by its stimulating effect on the duodenum, propels the bile onwards and thus prevents the Quinine forming an inert compound with the bile.

Whilst insisting on an initial purge, and more especially a calomel purge, I may here give a few short details of a case of Malaria in a lad, who lived in the West Indies, which was treated with Calomel and James' Powder, no Quinine being given until convalescence, owing to a temporary dearth of the latter drug. The patient, a negro lad of 16 years, who lived in the interior, had been in bed with fever for five days previous to my seeing him. Then he was lying on his back in a half delirious state, his extremities cold, his tongue caked and dry, with a rapid, weak pulse. The thermometer under the tongue registered 105° Fahrenheit. The following was his treatment:- No Quinine for the time being available - Ten grains of Calomel at once, four grains of Calomel with three grains of James' Powder every two hours for the next twelve hours. Thus thirty four grains of Calomel in all were administered in twelve hours. This produced neither diarrhoea, nor the slightest touch of the gums, but instead his temperature gradually fell, delirium abated, and in twenty-four hours from the last dose of Calomel his temperature was found to be normal. He was then given a saline purge and put on Quinine,

rapid recovery ensuing. In claiming the recovery of this lad in some extent to the germicide effects of Calomel, I do not forget the vis medicatrix naturae, nor the post hoc, propter hoc. This lad was to all intents in a dying condition, and from my experience of similar cases, I believe he would have died, had no remedy been administered to combat the materies morbi. I do not claim that the value of calomel as a germicide in Malaria approaches to that of Quinine, but that other drugs, besides the latter, can kill the parasite has been proved by the Austrian observer Mannaberg, and others. This observer adopted the plan followed by Laverau. To a series of slides of Malaria blood he dropped solutions of Quinine, and to other slides he dropped solutions of other germicide drugs, and as a control a series of slides untreated by drugs. After a short time, it was found that on the untreated slides the parasites were alive, whilst on the others they were all dead. From this it would appear that if the circulating blood was sufficiently charged with anyone of the many germicide drugs employed in the experiment, the result would be the death of the parasite, but in many instances the death of the host would co-incide, owing to the toxic power of the drug on the human organism, and it is here that Quinine stands prominently to the front, being harmless to the host and poisonous to the parasite. The modus operandi of Calomel I will not venture to state emphatically, but I may suggest that the hydrochloric acid of the stomach in conjunction with the sodium chloride of the tissues, may raise part of the mercurous salt

into the mercuric state, and that the nascent corrosive sublimate thus formed will find its way into the circulating blood, exerting only a minute toxic effect on the host, but yet sufficiently strong to kill the parasite, or at least to render the circulating fluid no longer a suitable nidus. As from the researches of Koch we learn that one part of Perchloride in a million, retards the growth of the anthrax bacilli. Sir Joseph Lister in the "Lancet" of November 9th, 1889, states that although corrosive sublimate precipitates albumen, the precipitate is not an albuminoid of Mercury, but that the bichloride retains its properties intact, the Albumen being only loosely associated with it; and further, that this precipitate is soluble in blood serum, is powerfully antiseptic and non-irritating. May not this theory explain the action of Calomel in Malaria?

Spontaneous cure:-

That in Malaria of a mild type patients may get well without treatment by drugs, or at most with the aid of a purge, is well known. And to illustrate this, I will relate a case which came under my notice a few weeks ago. A sailor was admitted into the Seaman's Hospital and the parasite demonstrated without difficulty. No quinine was administered as it was proposed to keep his blood for a demonstration before a Medical Society ten days later. At the expiration of this period, repeated and prolonged examinations of his blood failed to yield the parasite, and the man declared himself as feeling well. The spontaneous cure is probably due to the phagocytic

action of the microphages in the spleen and marrow, to numerous parasites remaining sterile, to the destructive action of the fever paroxysm, which shows itself in the disintegration of numerous immature and mature parasites, aided by rest in bed and efficient nourishment, and of course removal from fresh infection. (Mannaberg)

A fundamental principle in the treatment of disease is the removal of the cause, and as the essential factor of Malaria is a parasite in the blood, any line of treatment, then, which lays claim to being rational, must be so directed as to have a drug of a parasiticide nature in the circulating fluid, and thus combat and destroy the disease producing agency. When Malaria is mentioned, Quinine naturally suggests itself. I say naturally, for there is perhaps no fact so well established in therapentics as the efficacy of Quinine in this disease; this efficacy was said to be due to its "antiperiodic" action. Since the brilliant discovery of Laverau, the curative value of the salts of quinine has now been indubitably shown to be due to their parasiticide action, and the treatment by Quinine now rests on a scientific basis. All efforts are therefore directed towards cinchonising the parasite. The older writers waited until the Fever had abated before they administered the remedy, and for the milder forms this plan answered admirably, as during the intermission of Fever the blood was charged with Quinine, and thus in a condition to destroy the young parasites (which are the most vulnerable) on the bursting of the sporing bodies.. The young brood are thus killed in

statu nascendi, and thereby the attack which should follow is rendered impossible. However, this method is not applicable to fevers of a mixed character, and of a continued type, and he who would attain success must administer the remedy at once, no matter what the heat of the body may be. Professor Maclean writes emphatically, "I never waited for a remission, but gave Quinine at once. Practitioners who relax in their efforts to stop the exacerbation, who pause in the use of Quinine, while they apply routine remedies for this or that symptom, will have little success in the worst forms of Indian remittents."

In such cases where the state of the stomach would permit it, I generally begin the Quinine treatment by giving scruple doses of the sulphate, dissolved with the aid of a mineral acid, every four hours for the first twenty-four hours, and then less frequently, according to indications. In nervous patients, and there are many on the West Coast of Africa, who collapse almost at the beginning from sheer fright, I usually combine the quinine with hydrobromic acid. These large doses, as a rule, do not induce troublesome physiological action. But the vomiting and retching, especially in those addicted to the abuse of alcoholic stimulants, are so constant a feature that medication and aliment are frequently impossible per oram, and then resource is had per rectum. Similar doses are administered by the bowel, mixed with nourishment when necessary and the results are equally beneficial. In the more malignant forms, where it is imperative to cinchonise the parasite

at once, hypodermic medication is employed. The following solution, recommended by Vitali and Galignani may be most conveniently used. Chininum Muriat, 10 grammes, aqua dest. 7½ grammes, Acid Mur. dil. 2½ grammes. This solution contains approximately 11¼ grains in 16 minims.

Bacelli has recently introduced the intravenous injection of Quinine with much success for the gravest Malarial infections, in which the greatest possible concentration of the drug and the most rapid action is needed. He recommends it for cases of Malaria Comatosa, and he employs the following solution - Chininum Mur., one gramme, Natrium Chlorat 7½ centigrammes, Aqua dest., 10 grammes. The solution should be boiled and filtered, and injected directly through the disinfected skin into a vein in the arm.

Besides the administration of Quinine it is often necessary to exhibit other remedies to assuage the sufferings of the patient. Thus a full dose of antipyrin, or preferably Antefebrin will relieve the pain in the head and limbs, induce perspiration and promote sleep (insomnia being frequently most rebellious) and the patient awakes "feeling quite another man".

After all has been said and done, Quinine frequently fails, whether from imperfect action of the mucous membrane of the stomach and intestines, or of the subcutaneous connective tissue which delays absorption, or blocking of the cerebral capillaries with infested blood corpuscles, on account of which the parasites cannot come in contact with the quinine, or perhaps to an increased power of resistance on the

part of the species of the parasite as is seen in the crescentic forms, I know not, but the fact remains that in many regions of the Globe two-thirds of the mortality is caused by Malaria.